GABA Receptors and Alcohol

Introduction

In *Basal Ganglia,* we nebulously used inhibition and stimulation, represented by colored cables, to focus on dopamine. When we talked about the parasympathetic nervous system in General Pharmacology, we focused on acetylcholine. The same was true for skeletal muscle in General Physiology. Now, we focus on GABA, the main mechanism for hyperpolarization within the central nervous system.

We start with GABA receptors and the functional similarities between the ones we care about—$GABA_A$ receptors—and the familiar ionotropic nicotinic acetylcholine receptors. We briefly talk about $GABA_B$ and its actions, but we don't want you to focus on it now. We then talk about the physiologic antagonism between glutamate and GABA, and the role that astrocytes play in maintaining functional synapses. Then, the meat of the lesson—benzodiazepines, chronic GABA stimulation, and withdrawal syndromes. We round out the discussion by showing the similarities and differences between the effects of barbiturates and ethanol on the GABA system.

GABA Receptors in General

γ-aminobutyric acid (**GABA**) is an **inhibitory neurotransmitter**. There are three GABA receptor types: A, B, and C. $GABA_C$ receptors are found in the retina and will be discussed in the Special Senses island.

The $GABA_B$ receptor is a G protein-coupled receptor (GPCR) that is associated with G_i, leading to the inhibition of adenylyl cyclase and a reduction in cytoplasmic cAMP. That's no different from any other G_i protein-coupled receptor. But in the central nervous system, two GPCRs have effects in addition to the ones we've taught you. In truth, the other metabotropic GPCRs have more than just their α-subunit's effects. But those effects now matter at synapses. We want you to focus on $GABA_A$ receptors in this lesson. So, we'll say it succinctly here, and in greater detail when you get to pain tracts: the $GABA_B$ receptor is a GPCR that not only reduces cytoplasmic cAMP but also opens postsynaptic potassium channels (hyperpolarizing the postsynaptic cell) and blocks presynaptic voltage-gated calcium channels, thereby reducing the presynaptic release of excitatory vesicles.

$GABA_B$ and $GABA_C$ receptors are GPCRs. You don't care about them yet. We want you to know they exist. This isn't obligatory, and they do matter; they just are not where we want your focus right now. And because their mechanism is the same as μ receptors in the pain tracts, we'll fill in the details there. **$GABA_A$** receptors are like nicotinic acetylcholine receptors, except they bind GABA and conduct chloride. Here is the overview. In the next section, we'll go into $GABA_A$ receptors in detail.

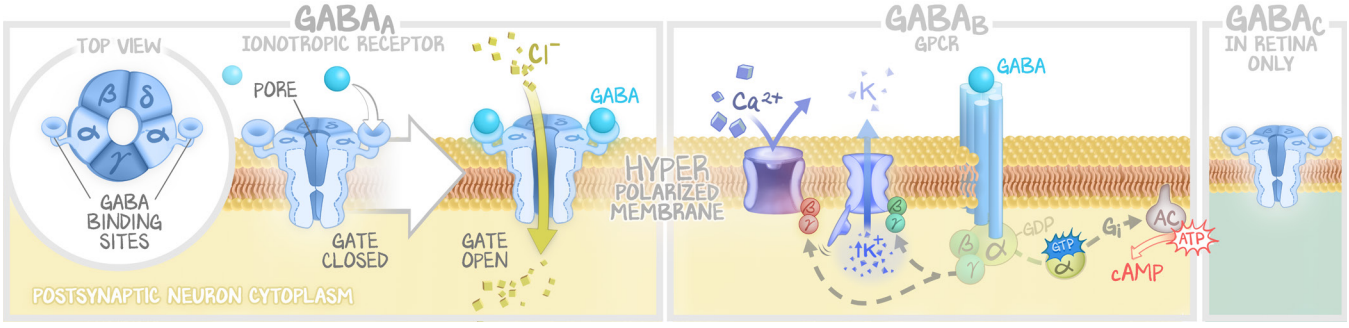

Figure 2.1: GABA receptors
(a) $GABA_A$ receptors are like the nicotinic acetylcholine receptors that you already know—molecules bind, gates open, ion conductance goes up. The difference is that $GABA_A$ receptors conduct chloride, hyperpolarizing the postsynaptic neuron. (b) Both $GABA_B$ and $GABA_C$ receptors are GPCRs that utilize G_i to reduce cAMP and have additional effects. More on this in Clinical Cortex #7: *Pain and Analgesic Tracts*.

$GABA_A$ Receptors

The $GABA_A$ receptor is an ionotropic receptor that belongs to the same superfamily as the ionotropic nicotinic acetylcholine receptors you saw in General Physiology, General Pharmacology, and . . . every organ system. That nicotinic acetylcholine receptor channel is the mechanism used at autonomic ganglia—sympathetic and parasympathetic alike. It is also the channel at the motor endplate. That channel is pentameric—it has five domains. There are **two α**, and **one** each of **β**, **γ**, and **λ**. When two molecules of acetylcholine bind to their binding sites, one on each of the α domains, the channel undergoes a conformational change, thus becoming permeable to ions—both **sodium and potassium**.

We dragged you through things that you already know so that we can explain $GABA_A$ receptors really easily. **GABA** binds to the **α** domains on $GABA_A$ receptors, making them permeable to **chloride**. Chloride is a negatively charged ion, the concentration gradient of which favors entry to the cell. Negative charges moving into the cell are an inhibitory signal, driving the membrane potential away from its threshold. In other words, the equilibrium potential for chloride is –64 mV, and as more channels open for longer durations, the membrane permeability to chloride increases, and the cell more quickly approaches chloride's equilibrium potential. Therefore, GABA drives inhibitory postsynaptic potentials (IPSP), hyperpolarizing the postsynaptic cell.

GABA is an inhibitory neurotransmitter. The GABA receptor is an inhibitory chloride channel.

What makes the $GABA_A$ receptor so special is that there are **binding sites for molecules** other than GABA. Medical science hasn't discovered what they are, but we have found ways to manipulate them. Sedative and anxiolytic medications—**benzodiazepines** and **barbiturates**—have their own endogenous binding sites separate from the GABA-binding sites. On their own (i.e., in experimental conditions where GABA isn't present), these drug classes **don't do anything**. But when GABA is around (either experimentally or in a person), benzodiazepines **increase the frequency** with which GABA channels open, and barbiturates **increase the duration** for which they are open. Either way, there is more membrane permeability and, therefore, more inhibition.

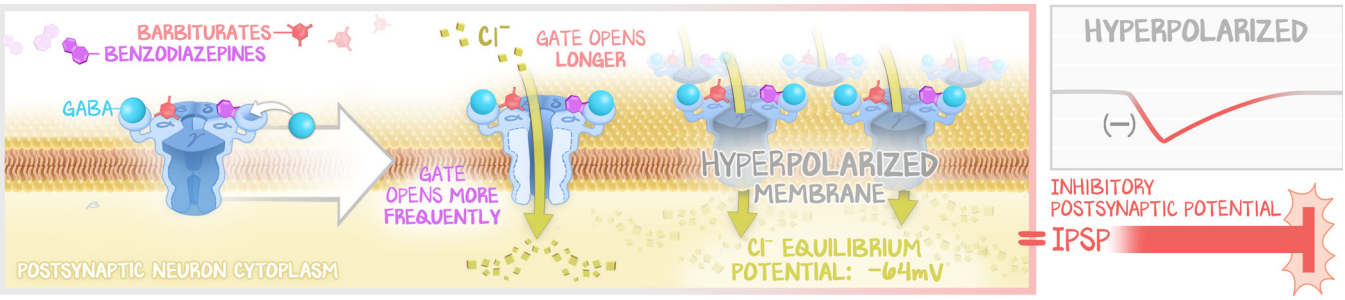

Figure 2.2: $GABA_A$ Receptors Are Just Like nACh Receptors, Except with Chloride Ions
Neither benzodiazepines nor barbiturates are capable of activating the $GABA_A$ receptor. They both bind to the receptor at their own binding site, independent of the GABA binding site. When GABA is present (as in, when a human ingests a barbiturate or benzodiazepine), the GABA signal is increased by the presence of the drug. Barbs increase the duration that the channel is open, whereas benzos increase the frequency with which it opens. Either way, more chloride conductance, more GABA signal, more inhibition of the postsynaptic membrane.

Subtypes of $GABA_A$ Receptors

Time for a change in nomenclature. The $GABA_A$ receptor has drawn so much attention in the pharmaceutical field that it is usually referred to as the benzodiazepine (BZ) receptor, leading to much confusion, especially after peripheral non-GABA benzodiazepine-activated receptors were discovered. You are definitely going to hear and see references to BZ1 and BZ2. The IUPHAR recommends the discontinuation of all previous nomenclature because there are no benzodiazepine receptors, only receptors with **benzodiazepine sites** (their recommended nomenclature) or benzodiazepine-binding domains. We are still going to use shorthand—BZ1 and BZ2—because it so clearly demonstrates what we're talking about internally. We also do this so that when you see all the literature that uses those terms, you aren't caught off guard. But we are not going to say "BZ1 receptors" (inaccurate); instead, we are going to use the transitive property:

BZ1 means "the $GABA_A$ receptor with the **α_1-isoform** benzodiazepine-binding domain."
BZ2 means "the $GABA_A$ receptor with the **α_2-isoform** benzodiazepine-binding domain."
BZ1 is highly concentrated in the **cortex**, **thalamus**, and **cerebellum**. BZ1 is responsible for the **sedative effects**, **anterograde amnesia,** and **ataxia** associated with benzodiazepines. Approximately 60% of $GABA_A$ receptors are BZ1. Therefore, amnesia and ataxia are common side effects of benzos.

BZ2 is highly concentrated in the **limbic system** (thought to produce the **anxiolytic** effect of benzodiazepines) as well as **motor neurons** and the **dorsal horn** of the spinal cord (thought to produce their **myorelaxant effects**).

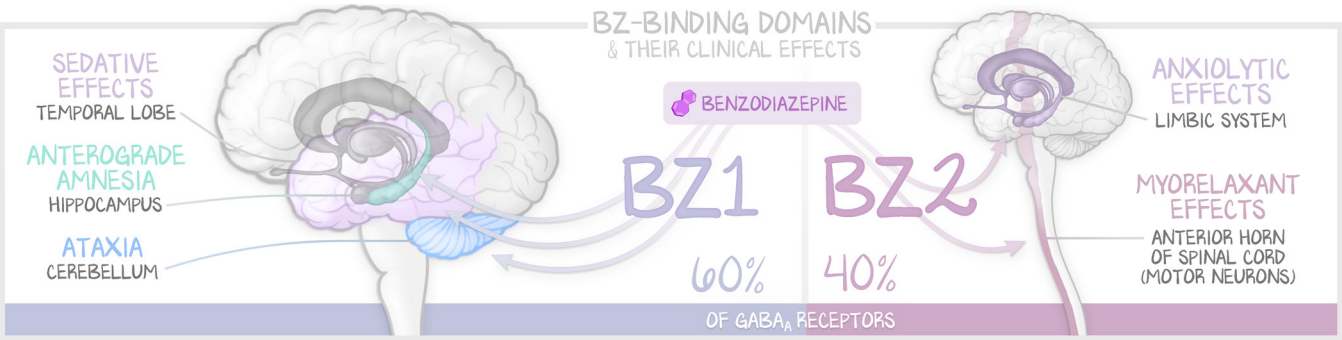

Figure 2.3: BZ-Binding Domains, Their Locations in the Brain, and Their Consequences
BZ1s cause ataxia, amnesia, and sedation; BZ2s induce muscle relaxation anxiolysis.

GABA and Glutamate

These are not the only physiological antagonists in the brain, but they are commonly the only two used to describe the pathogenesis of alcohol and benzodiazepine withdrawal.

$GABA_A$, you know well—chloride channel, binds GABA, also binds benzodiazepines, inhibitory. Glutamate, we haven't talked about in any detail. **Glutamate receptors** are the most common excitatory receptors in the central nervous system; therefore, **glutamate** itself is the most common **excitatory** signal used in the CNS. The "glutamate receptor" is really a family of receptors that bind glutamate. Much like the $GABA_B$ receptor, you don't need to know the details of these glutamate receptors. There are AMPA glutamate receptors and NMDA glutamate receptors. AMPA conducts calcium and depolarizes the postsynaptic cell. This step must happen for NMDA receptors to open. NMDA receptors conduct calcium, potassium, and sodium. And just like with the nAChR, even though potassium leaving the cell is a hyperpolarizing stimulus, the net voltage change is depolarizing.

And guess what? AMPA and NMDA are also both pentameric ligand-gated ion channels, just like nAChR and $GABA_AR$.

In the resting state, without disease or medications on board, there is a balance. The CNS is excitable enough to function, but not so excitable as to cause dysfunction. This balance will change as we discuss alcohol, benzodiazepines, and barbiturates. But first, astrocytes.

Astrocytes and GABA-Glutamate

Amongst their various roles (see Neuroscience: Cortex #2: *The Normal CNS: Cells, Fascicles, and Meninges*), one role of astrocytes is the management of neurotransmitters and augmentation of synapses. And while this next bit is a huge oversimplification, this teaching technique helps to bring functional clarity to the CNS. There is physiologic antagonism between GABA and glutamate. **GABA is inhibitory** and causes **hyperpolarization,** while **glutamate is stimulatory** and causes **depolarization**. Visualize every synapse in the CNS as having four cells: the presynaptic glutamate-releasing neuron, the presynaptic GABA-releasing neuron, the postsynaptic neuron with both glutamate and GABA receptors, and an astrocyte. GABA-releasing neurons make GABA from **glutamine**, package GABA in vesicles, and when depolarized, release GABA into the synaptic cleft via exocytosis. Those same GABA-releasing neurons can also **reuptake GABA**. Conversely, the glutamate-releasing neuron makes glutamate from **glutamine**, packages glutamate in vesicles, and when depolarized, releases glutamate into the synaptic cleft via exocytosis. The same glutamate-releasing neurons can also **reuptake glutamate**.

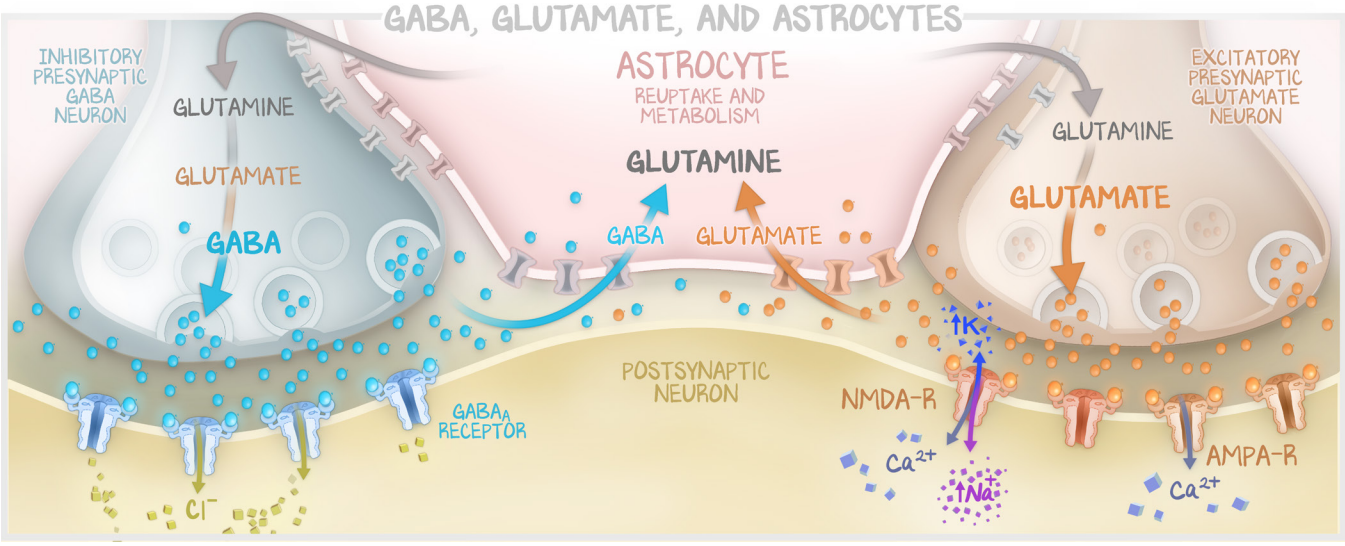

Figure 2.4: GABA, Glutamate, and Astrocytes, Oh My
Glutamate is excitatory, inducing a depolarization by activation of AMPA and NMDA glutamate receptors. The details of their interaction with each other is beyond the scope of this course. GABA activates $GABA_A$, which leads to a hyperpolarization. Whether the postsynaptic neuron will depolarize or not is based on the overall average of the inhibition and excitation. Physiologic antagonism results in two competing systems that don't interact with each other (glutamate neurons release glutamate and activate glutamate receptors; GABA neurons release GABA and activate GABA receptors). The astrocytes are the referees of this competition, capable of neurotransmitter uptake as well, and are the source of glutamine that both neurons require to make more neurotransmitter.

Here's the thing. **Neither presynaptic neuron knows how to make glutamine**, the precursor molecule from which both glutamate and GABA are synthesized. The cells that know how are **astrocytes.** Astrocytes can uptake GABA or glutamate from the synaptic cleft, metabolize those neurotransmitters and degrade them to inactive metabolites, or turn them into **glutamine**. Astrocytes are connected to

each other by gap junctions, enabling them to move molecules (to other synapses) and also to decide which presynaptic axon gets the glutamine—a regulation of activity.

Astrocytes express a wide variety of ionotropic and metabotropic neurotransmitter receptors that are similar or identical to those present on neuronal membranes. As in neurons, activation of these receptors can open ion channels or generate second messenger signaling. In most astrocytes, **glutamate** produces **depolarization** by increasing conductance to cations (Na^+, Ca^{2+}, and K^+), whereas **GABA** hyperpolarizes cells by opening **Cl^-** channels. It is likely but not proven that the activation of GABA or glutamate receptors on astrocytes is the signal both to take up neurotransmitters from the synaptic cleft and to release the precursor glutamine.

But who to give the glutamine to? It is unlikely that within the intensely regulated microenvironment of the synaptic cleft, which the astrocytes meticulously maintain, that astrocytes are merely present to uptake excess neurotransmitter left behind by either neuron. Rather, it is likely that astrocytes monitor how much GABA and how much glutamate is being released into the cleft—astrocytes have those receptors, too. The known mechanisms of alterations of postsynaptic neuron receptors (upregulating glutamate receptors or downregulating GABA receptors). Likely, astrocytes are also modulating presynaptic vesicles, informed by the same signal as the postsynaptic neuron ($GABA_AR$, Glutamate Receptor).

What $GABA_A$ Receptor Stimulation Does Long Term, and What Happens When It Suddenly Stops

Tolerance is when one needs a higher concentration of a drug to experience its intended effect. **Dependence** is when one experiences physical or psychological withdrawal symptoms upon abruptly stopping use. Benzodiazepines are meant to be used for acute anxiolysis. You should not treat chronic anxiety disorder with benzodiazepines. However, some patients are put on chronic benzodiazepine doses. Initially, the intended effect is achieved with a low dose. Whether they are used for their intended purpose or abused, tolerance will develop, and a higher dose will be needed to achieve the same effect. This isn't meant to make anyone on benzodiazepines feel poorly; it's just that this is a real possibility.

The risk of developing tolerance is higher when benzos are used chronically or abused. The reason for that is the changes in the GABA-glutamine microenvironment. Excessive GABA receptor inhibition is met with synaptic plasticity—**GABA receptor expression decreases**, whereas **glutamate receptor expression increases**. A new balance is found between [GABA+benzo] and glutamate. As the cycle continues, the exogenous benzodiazepine dosage increases, and, to restore the balance, glutamate receptors are upregulated and GABA receptors are downregulated. This cycle happens over and over, always requiring a higher dose to find the intended effect, and always making the system more dependent on that benzo.

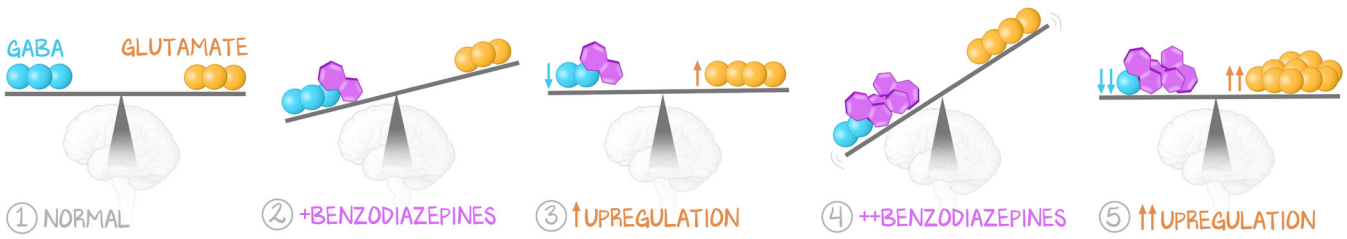

Figure 2.5: Chronic Stimulation Leads to Imbalance
There will always be a balance between excitatory and inhibitory signals. It's how the central nervous system needs it to be. A patient may take medication to achieve an intended effect. If that medication is a benzodiazepine, it will generate a stronger inhibitory signal. The body will balance the system; less endogenous inhibitory signal, more endogenous excitatory signal. The patient requires more and more drug to achieve the desired effect. Each time the dose is stepped up, endogenous inhibition is decremented, while endogenous excitation is incremented. Over and over, the cycle repeats.

When the patient no longer provides that dose of benzo to the system, what they are left with is greatly upregulated glutamate receptors and greatly downregulated GABA receptors. It was a gradual shift to this state, but now with the abrupt withdrawal of the benzo, immense, unrestricted excitation occurs. The system needs time to reset itself by tapering off the benzodiazepine. Without that taper, there are withdrawal symptoms. **Withdrawal symptoms** due to benzodiazepines all extend from excess **excitation**.

In clinicals, you are going to see this next discussion from the perspective of alcohol withdrawal because alcohol withdrawal is far more common than benzodiazepine withdrawal. We started with $GABA_A$ receptor physiology and introduced benzodiazepines first because benzodiazepine physiology is "cleaner" than that of alcohol. Benzodiazepines affect only $GABA_A$ receptors. Alcohol is a "dirtier" drug because it impacts so many receptors. But good news! Because the withdrawal symptoms are nearly identical in both cases, we can teach a common "withdrawal" from the perspective of benzos.

The patient stops taking benzos. The benzo wears off gradually over the course of the first day. That isn't long enough for the GABA-glutamate imbalance to be repaired, but it's slow enough that symptoms generally don't present until well into the first day. And you won't see this next part in most textbooks because it isn't ALWAYS exactly this progression, but what this provides is a visualization that aids in comprehension rather than a list of symptoms that can occur at any time and in any order. And there isn't a timeline, no "*at this many hours this symptom shows up.*" No matter what you read or are told, symptom progression is far more reliable than the exact number of hours since the last drink. It depends on how much and for how long the GABA stimulation was around, and how abrupt the withdrawal was.

Visualize a man in a hospital gown, sitting in a bed in the ED. *He's calm, dry, and bored*. Then the withdrawal symptoms begin. The motor outputs—autonomics first, then skeletal muscle—become more active. The sympathetics get revved up. α_1 stimulation clamps down on the vasculature—his diastolic pressure goes up. More β_1 stimulation induces a faster heart rate. **Diastolic hypertension** and **tachycardia** are usually the first signs, the earliest symptoms of withdrawal. *That man is still sitting there, dry and calm, unaware of his increasing pressures.* Hours go by. He's in the ED for a lacerated big toe. What could be taking so long? As the sympathetics are increasingly activated, α_1 stimulation induces his sweat glands to produce more sweat, causing intense **diaphoresis**—drenching sweats. *The patient is calm, soaking wet, and wondering why it's so hot in here.* It's not hot. That's the second symptom. Then the skeletal muscle tracts activate. First, the patient develops a little twitch in his fingers and hands; then, he notices that they are shaking uncontrollably—**shaking tremors**. *He's wet, still with it, but definitely concerned about not being able to control his hands.* Then sensory activates. **Anxiety** and **restlessness** are an ominous sign. Phrases like "bugging out" or "trying to get out of my skin" signal that the whole nervous system is revved up. *He's wet, shaking, alert, but looking back and forth; his breathing is faster; he's visibly uncomfortable staying in bed.* Then **nausea** and **visual or tactile hallucinations** (not the auditory hallucinations of schizophrenia) arrive. *He's wet, shaking, and trying to touch something in the air that isn't there, scratching his arms to get off the bugs that aren't there.* When he becomes encephalopathic (altered, confused, delirious), seizures are around the corner. *He's soaked, shaking, and tossing around on the bed; he stretches out across the bed, perpendicular to how he should be. He moans meaningless sounds.* Then, **seizure**. *He has alternating tonic and clonic contractions.*

Patients can experience symptoms in any order or have some but not all of the symptoms. The CIWA score is probably the most subjective-objective test. CIWA is a scored evaluation (objective) but asks the patient (and the examiner) a subjective question ("*how bad is the headache?*"). When one examiner repeats the CIWA test on one patient, the trend is extremely reliable. When two different examiners perform the test on one patient, even one after the other, the interoperator values are poor. Therefore, it isn't something worth memorizing, which is why we haven't provided it to you. It is immensely important and useful for the nurse monitoring a patient in withdrawal in the ICU in determining if more benzos or needed or if they can back off based on protocol. The CIWA score asks about anxiety, headache, and nausea/vomiting. It is a marker for nursing staff to use (especially in the ICU) to track a

patient's progress. But if you did the thought exercise and really saw the changes, with the addition of symptoms escalating towards seizing, it doesn't matter if you remember nausea before anxiety or anxiety before nausea. Vital signs, sweats, shakes (motor). Anxiety, nausea, hallucinations (sensory). Then, seizure (whole brain).

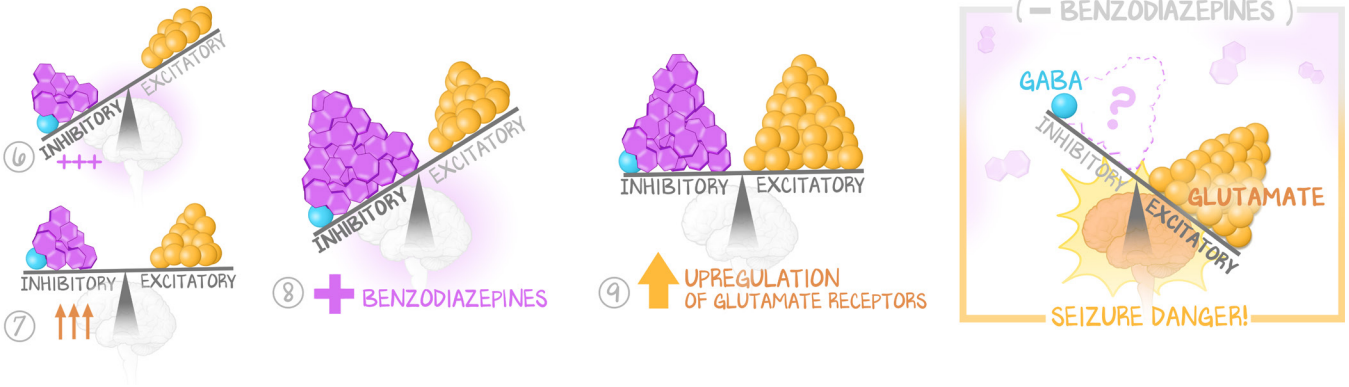

Figure 2.6: Acute Withdrawal Leaves the Patient Vulnerable to Imbalance
When the endogenous inhibition signal is downregulated and the endogenous excitatory signal upregulated, there is a balance, but a precarious one. Should the drug be abruptly withdrawn, there will be an intense excitatory signal, which can lead to withdrawal symptoms, and ultimately seizure.

Benzodiazepines

Not all benzodiazepines interact with the same type of benzodiazepine-binding site or with equal affinity to a specific receptor. These differences in α-subunit isoforms, receptor-type affinity, and location within the central nervous system account for the different effects of the various benzodiazepines. It can get quite complex, as there are so many benzodiazepines. You must be able to recognize which are short acting, and which are longer acting. Those that are short acting have frequent dosing requirements and are usually used in acute situations. Chronic benzodiazepine use is not always inappropriate (there are legitimate uses for them), it's just that there are better medications to manage whatever it is the patient is on a benzo for (such as an SNRI for chronic anxiety). They can be used as an adjunct, and we don't want you hearing "benzos are bad," but because they have addictive potential and can lead to dependence and tolerance, they shouldn't be seen as routine options for chronic disease. They are schedule IV—low potential for abuse and low risk of dependence. That's true, but only when used acutely, and not purposefully prescribing them around the clock.

The **short-acting** benzos are rapid-on, rapid-off. They have a **short time to onset** and a **short half-life**. This makes them the **most addictive** and gives them the **highest risk of withdrawal seizure**. They have a definitive use inpatient—controlling seizures, aborting anxiety, (off-label use) aborting nausea, and for sedation during short procedures. They have a legitimate use for patients who have triggerable anxiety—a single prophylactic dose before boarding a plane for someone with a fear of flying. The danger is when patients end up using them all day long. Even if used as prescribed (not abused), there is a potential for withdrawal seizure. There are many benzos, and we want you familiar with the names patients will use. Almost never do we allow trade names into our curriculum. For medications that can cause dependence, tolerance, and life-threatening withdrawal seizures, however, we felt it ethically sound to empower you to recognize these medications. You should recognize these four: **alprazolam** (trade name Xanax), **midazolam** (trade name Versed), **diazepam** (trade name Valium), and **lorazepam** (trade name Ativan). Although lorazepam is technically a "medium-on, medium-off," it is the preferred agent for treating alcohol withdrawal symptoms. Midazolam is the fastest on, fastest off, and is usually given intravenously before procedures.

Benzos should be used to treat acute anxiety (**panic attack**) and not chronic anxiety. Benzos should also be used as alcohol-withdrawal prophylaxis. In someone with a high risk of alcohol withdrawal, a slow-onset, longer-duration (because the slowest benzo is prescribed every 8 hours) benzo, such as **chlordiazepoxide**, is prescribed and scheduled with a descending dosage over 3 days. If symptoms do not occur by the end of day 3, and no additional intravenous medication is required, the benzo can be stopped. In addition to the scheduled doses, there is a standing order for as-needed intravenous doses of **lorazepam**. The decision to administer these as-needed doses is based on nursing assessment. If lorazepam is needed at any given scheduled dose of chlordiazepoxide, do not advance the de-escalation. Benzos are also used for **conscious sedation** during invasive procedures that do not require general anesthesia (colonoscopy, endoscopy, and bronchoscopy are good examples).

Benzos cause **anterograde amnesia**—the patient doesn't remember the procedure or the ride home. Taking too many can lead to **respiratory depression**. In a patient who is in withdrawal and showing withdrawal symptoms, there is no upper limit of benzodiazepine dosage. The as-needed intravenous medication is titrated (usually by the nurse). Never use a benzodiazepine infusion, because if the person isn't suffering from excitation symptoms, or a benzo is given despite no active symptoms, ongoing depression of the CNS will lead to respiratory depression and death.

If a person attempts suicide with a known **benzodiazepine overdose** and has respiratory depression, they should be intubated and the benzo overdose allowed to wear off. **Flumazenil** is a medication that can reverse benzodiazepine overdose, much like naloxone does for opiates. But whereas the consequence of reversing opiates is pain, giving flumazenil in any scenario other than the one exact right setting (known benzodiazepine overdose) **induces seizures**. If there is a licensing exam question about what medication to use for benzo overdose, pick flumazenil. But if you try to order flumazenil on a patient, you can bet your attending is gonna have a chat.

Non-Benzodiazepine Hypnotics = Sleep Aids

Zolpidem is a highly selective agent that only activates BZ1, achieving the sedation effects without impacting BZ2. But even though it isn't a benzodiazepine, because it activates BZ1 so well, it will still induce anterograde amnesia and cerebellar ataxia. A once-nightly medication doesn't sound so bad. And the patient is going to sleep anyway, so what's wrong with a little BZ1 activation to help them fall asleep?

Dependence.

There is, of course, some risk of seizure, but, used appropriately, zolpidem doesn't result in withdrawal symptoms. But dependence is not a healthy thing. Benzos reduce REM sleep (meaning the sleep isn't as restful), and crippling **insomnia** arises as a result of chronic use. It is okay to use zolpidem for a short course, but it should not be used chronically.

Barbiturates

Since the advent of antiepileptic drugs and benzodiazepines, barbiturates have had a limited role in modern medicine. They definitely have no role in outpatient medicine, but they remain used in the operating room for quick procedures. **Thiopental** is used in such a way. However, if things do not go well, and a repeat dose is required, it can reach toxic levels for a much longer period than expected. Because the initial loading dose is rapidly distributed into **fatty tissue** (out of the blood but still in the patient), it acts as a **reservoir**, slowly leeching back into the bloodstream—this effect is desired. When the reservoir stops having enough to maintain the sedation (still leeching out but not having an effect), the patient wakes up. But if a second dose is needed, it saturates these reservoirs and forces a lot of thiopental into the brain. The patient may have sustained coma and depressed respiratory function for hours or days.

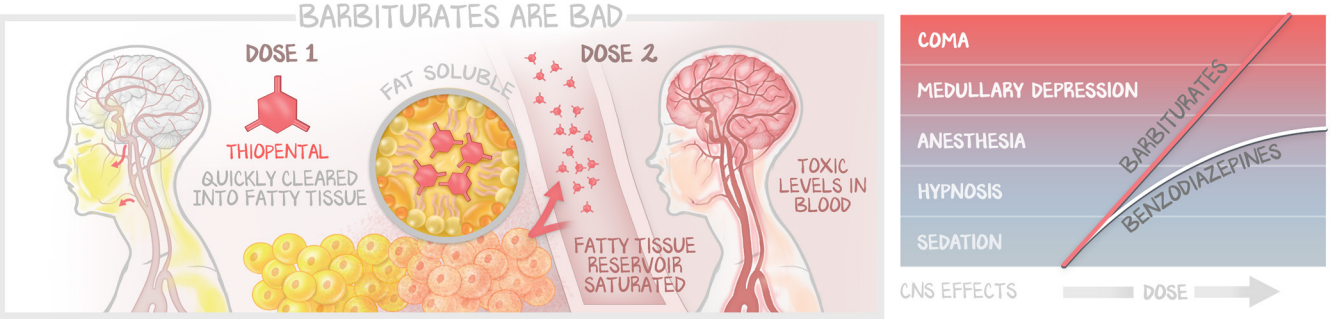

Figure 2.7: Barbiturates Are Bad
Although they have the same effects as benzodiazepines, the safety profile of barbiturates is worse. Increasing the dose increases toxicity nearly linearly. Thiopental is a useful anesthetic agent when a procedure is short, and full generalized anesthesia and intubation aren't required. However, if a second dose is administered, the resultant respiratory depression may require intubation and ventilation while it wears off.

Phenobarbital is the only medication you may see in the outpatient setting. It is used as an anticonvulsant. It is never the first-line medication and never the preferred treatment. It should only be used for seizures in a patient with severe disease and as an adjunct to other failed medications.

Barbiturates do have a place in medical practice today. They are used by providers of medicine who specialize in seizure treatment (neurologists), and infrequently for anesthesia. They are not in general practice. They are an older and more dangerous version of benzodiazepines. This isn't a class that should be eradicated from medicine but should be considered only in very specific conditions.

Alcohol

Medical science synthesized benzodiazepines based on the GABA receptor. They were tailored to bind to benzodiazepine-binding domains and nothing else. Any other action is a side effect. So, benzodiazepines are said to be **clean**—they target a specific receptor with a specific intended effect.

Ethyl alcohol, aka **ethanol**, has been known in cultures around the world for thousands of years. Most cultures discovered how to make it by fermenting whatever local food was available—rice, honey, wheat, barley, grapes—and to ingest it for an intended effect. But ethanol was not synthesized to fit a binding domain; it was made by bacteria fermenting sugar. It just so happens that ethanol is merely one of many **alcohols** (methanol, ethylene glycol, and isoproterenol) that can stimulate $GABA_A$ receptors. Drink too much ethanol, and you might "black out," and not remember the rest of the night. That's **anterograde amnesia**. When intoxicated, people may stumble, lose coordination, or slur their words. Those would be **cerebellar signs**. People "have a drink to unwind," the **anxiolytic** effects of BZ2 activation.

But alcohols are **dirty** drugs. Yes, they do share the activation of the $GABA_A$ receptor with benzos. But alcohols do a lot more than just stimulate $GABA_AR$, which leads to unpleasant side effects. First, alcohol both **stimulates $GABA_A$ receptors** and **inhibits glutamate receptors**. The postsynaptic neurons do the same following a dose of alcohol as following a dose of benzos—downregulate $GABA_A$ receptors, upregulate NMDA glutamate receptors. But under the influence of chronic alcohol consumption, the effects are amplified—even fewer $GABA_A$ receptors and even more NMDA glutamate receptors. In addition, there is an increase in channel conductance to cations. It isn't just more glutamate receptors; it's a lot more glutamate receptors that are even better at being excitatory.

Hangovers aren't associated with GABA or glutamate. That would be your liver converting alcohol to aldehyde, which your brain does not like. Drink too much one night, and you might have uncontrolled vomiting. That isn't GABA, either. The point is that alcohol is a much worse benzodiazepine with many unwanted side effects. The ones that matter (as uncomfortable as blacking out or throwing up might be, they usually don't kill) relate to GABA and withdrawal.

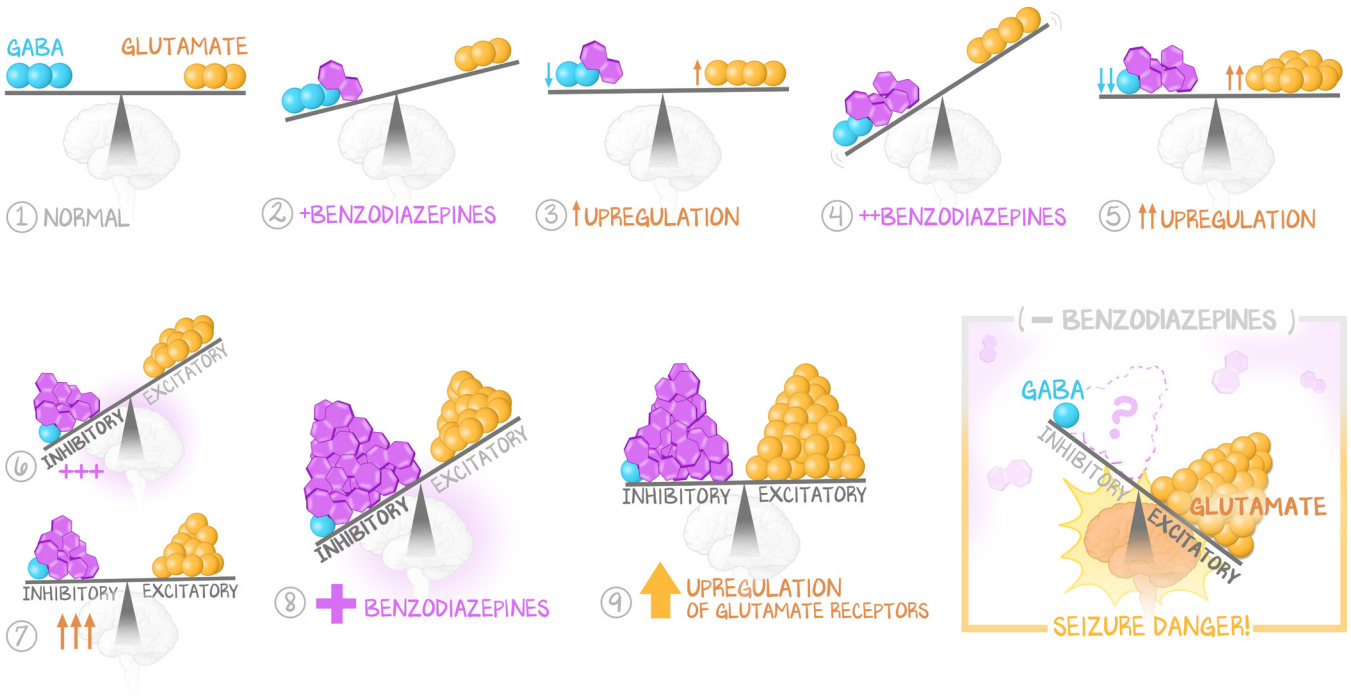

Figure 2.8: Remember This?
Benzos induce tolerance and dependence and can cause withdrawal. Ethyl alcohol is worse. Wherever there is a purple benzo, just replace it with two EtOH (both equal in size). Although benzodiazepine withdrawal is a real thing, far more often, benzos are used to treat alcohol withdrawal. This is the exact same image as above because alcohol does the same thing, only worse.

Ethanol comes up throughout the course, especially in the Gastroenterology module, as a cause of acute alcoholic hepatitis and cirrhosis. We want to stay focused on how similar ethanol is to benzodiazepines, but alcohol is easier to access and the withdrawal syndrome is generally more severe. The treatment is the same—oral benzos on a schedule, lorazepam intravenously as needed. This lesson isn't about addiction or the people these physiologic mechanisms affect. It's focused on the physiology.

Chronic Alcohol Consumption Causes Structural Lesions

Way back in Biochemistry: Metabolism #4: *Pyruvate Dehydrogenase*, we taught you about thiamine deficiency. Now we're at it again from the perspective of the brain rather than that of the metabolic enzymes. **Thiamine (B_1)** is needed for pyruvate dehydrogenase (the enzyme that makes acetyl CoA in the mitochondria) and isocitrate dehydrogenase (the rate-limiting step of the citric acid cycle which uses acetyl CoA to make ATP). **Ethanol inhibits the absorption of thiamine.** In chronic alcoholics who consume most of their calories through alcohol (not enough thiamine ingested), a B_1 deficiency may result. In the brain, that leads to Wernicke-Korsakoff syndrome, a spectrum from **reversible encephalopathy** (Wernicke encephalopathy) to **irreversible destruction** of the brain parenchyma. The reversible encephalopathy presents as "a drunk patient who didn't drink"—ataxia, nystagmus, confusion. The irreversible damage leads to ataxia, nystagmus, confusion, and **dementia**, characterized by short-term memory loss and confabulation.

Alcohol is a cerebellar **vermis toxin**. Chronic alcohol use can lead to the destruction of the vermis of the cerebellum, resulting in permanent ataxia and dyscoordination. Alcohol is a **neuronal toxin**. Chronic alcohol use can lead to **diffuse atrophy** of the brain, with resultant compensatory hydrocephalus ex vacuo. The loss of the cerebellum and atrophy of the cortex are visible on MRI and at autopsy, and the damage cannot be reversed.

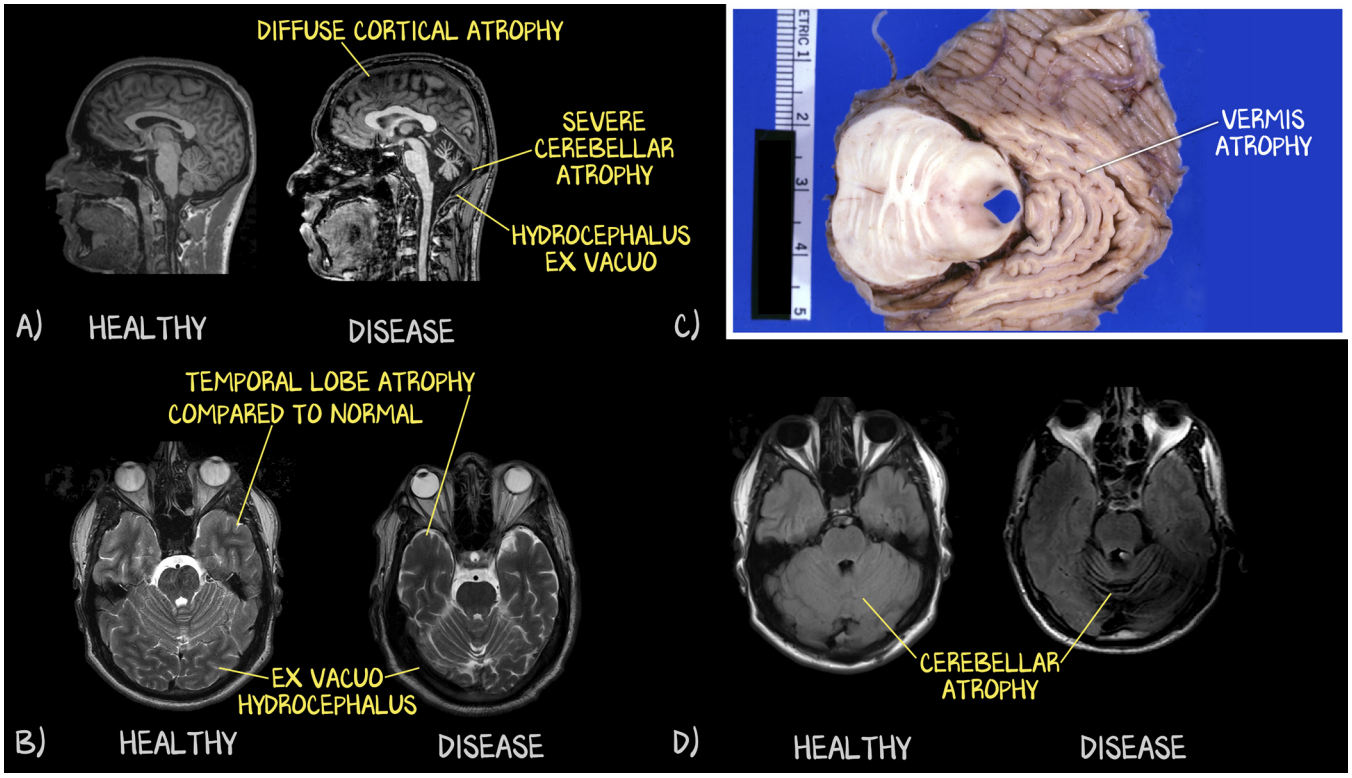

Figure 2.9: Impact of Alcohol on the Central Nervous System
(a) Mid-sagittal T1-weighted MRI showing diffuse cortical atrophy, severe cerebellar atrophy, and subsequent hydrocephalus ex vacuo. (b) T2-weighted axial MRI showing shrunken temporal lobes, hydrocephalus ex vacuo, and gaps in the cerebellar folds. (c) A gross specimen of vermis atrophy, with clear separation of the vermis layers, not normally seen. (d) T1-weighted axial MRIs showing the difference between a healthy cerebellum and one with obvious gaps between the cerebellar folds.

EtOH in moderation has been reported to increase high-density lipoprotein (HDL) levels. Sure. But a metabolic profile that is otherwise normal with a high HDL or a poor metabolic profile with a high HDL indicates a patient who is using alcohol inappropriately. Mediterranean diets, which include modest wine consumption, probably don't derive their benefit from alcohol, but rather from the paucity of red meat and abundance of vegetables. Telling all patients that alcohol should be strictly avoided is inappropriate. Telling all patients that alcohol might be healthy is also inappropriate (the hearer may interpret that as "I can have alcohol" while missing the intended meaning: "limit yourself"). Ethanol is a part of life in every culture on the planet, so if you're going to join in, do so in moderation.

Alcohols That Are Not Ethanol

These next few alcohols are those that also have the hypnotic-sedative effect of BZ1 activation, so ingesting them will induce the desired effects. But just like ethanol, their metabolites are toxic. For alcohols other than ethanol, their metabolites are so toxic that, if ingested, they are going to cause more than the intended effects and more damage than ethanol does. Whatever the reason they're ingested (suicide attempt, baby gets at the antifreeze [which is sweet], accidental ingestion, or someone just desperate for alcohol), they will have deleterious side effects.

Methanol is why you should not drink moonshine (actual self-made, self-distilled moonshine, not the brand moonshine). Methanol's metabolite is formate (formic acid), which preferentially destroys the retinal ganglia, leading to blindness. If someone offers you a sketchy shot and you fear it might be methanol, just light it on fire. Ethanol burns with a gentle, rippling blue flame. Methanol burns like a lo, with a bright white flame that leaps off the glass.

Ethylene glycol is a common toxic exposure. It is used in antifreeze formulations. Antifreeze is often brightly colored and tastes sweet. This is a prime recipe for unintentional ingestion by children. It is also very accessible—available at every gas station. Ethylene glycol will activate BZ1 and deliver the intended effect. But the metabolite of ethylene glycol metabolism—oxalate—is a component of the most common cause of kidney stones—calcium oxalate. Acutely, calcium is not reabsorbed by the renal tubule, so hypocalcemia may be present. But the worst outcome is the formation of **calcium oxalate stones** and **obstructive uropathy**, leading to renal failure. Under Wood's lamp, the urine will glow green. The goal is to get the liver's alcohol dehydrogenase to focus on something else. Acute alcohol or, more appropriately, **fomepizole**, can be administered. Alcohol dehydrogenase has a higher affinity for ethanol and fomepizole than for ethylene glycol. As ethylene glycol cannot be processed by alcohol dehydrogenase, other lower-affinity enzymes metabolize it to something else that isn't oxalate.

Isopropyl alcohol is "rubbing alcohol," used as a disinfectant and solvent in labs. The typical isopropyl alcohol available in stores is 70% alcohol, 30% water. Industrial isopropyl alcohol is 99% alcohol. It, like ethanol, will activate BZ1 and have the desired effect. Isopropyl alcohol's metabolite is a **ketone,** not an aldehyde. Acetone, its metabolite, is osmotically active but not acidic. The hallmark is **marked ketonemia** and **ketonuria** in the **absence** of metabolic acidosis, but with the presence of an osmolar gap. Because the effects are generally less toxic than the others, treatment is usually supportive.

Citations

Figures 2.9a, 2.9b, 2.9d: Courtesy of Radiopaedia.

Figure 2.9c: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.

